CLAIMS

1.   An in vivo screening method for predicting whether or not a test compound is capable of improving the memory/learning dysfunctions by schizophrenia, wherein said method comprises a step of evaluating the memory/learning functions by employing a model showing glutamic acid N-methyl-D-aspartate (NMDA) type receptor hypofunction as an animal model for schizophrenia, and a reference memory task.

2.   The method according to claim 1, wherein the reference memory task is a passive avoidance task, an active avoidance task, a water maze task, a radial maze task, a T or Y maze task, a place recognition task, an object recognition task, an autoshaping learning task, or a lever-pressing task.

3.   The method according to claim 1, wherein the reference memory task is composed of two sessions of training and testing, and in the training session the animals are made to learn either of the tasks described in claim 2 and to acquire the memory of said task, and in the testing session being carried out after a prescribed period from the training session, the retention and retrieval ability of said memory of the animals are quantified.

4.   The method according to claim 1, wherein the model showing an NMDA type receptor hypofunction is produced by administering a compound having an NMDA type receptor antagonistic activity, e.g., MK-801, phencyclidine (PCP), ketamine, or a derivative thereof, to the animals in both of the training session and the testing session of the reference memory task, or by chronically administering said compound or a derivative thereof to the animals during the period including the training session and the testing session.

5.   The method according to claim 1, wherein the model showing an

NMDA type receptor hypofunction is an animal model associated with an NMDA type receptor hypofunction due to variation, overexpression, or deficiency of gene of constitutive proteins or relevant proteins of an NMDA type receptor in both of the training session and the testing session of the reference memory task.

6. A therapeutic agent for the memory/learning dysfunctions by schizophrenia, which comprises a substance selected by a screening method as set forth in any one of claims 1 to 5 as an active ingredient.

7. A therapeutic agent for the memory/learning dysfunctions by schizophrenia, which comprises a serotonin 5-HT 1A antagonist selected by a screening method as set forth in any one of claims 1 to 5 as an active ingredient.

8. A therapeutic agent for the memory/learning dysfunctions by schizophrenia, which comprises a choline acetylase inhibitor selected by a screening method as set forth in any one of claims 1 to 5 as an active ingredient.

9. A therapeutic agent for the memory/learning dysfunctions by schizophrenia, which comprises aricept as an active ingredient.

10. A therapeutic agent for the memory/learning dysfunctions by schizophrenia, which comprises quetiapine as an active ingredient.

11. The therapeutic agent for the memory/learning dysfunctions by schizophrenia according to claim 10, which comprises as an active ingredient quetiapine in a daily dose of 5 to 270 mg.

12. The therapeutic agent for the memory/learning dysfunctions by schizophrenia according to claim 10, which comprises as an active ingredient quetiapine in a daily dose of 15 to 90 mg.

13. A therapeutic agent for the memory/learning dysfunctions by schizophrenia, which comprises clozapine as an active ingredient.

14. The therapeutic agent for the memory/learning dysfunctions by

schizophrenia according to claim 13, which comprises as an active

ingredient clozapine in a daily dose of 0.2 to 34.5 mg.

15. The therapeutic agent for the memory/learning dysfunctions by

schizophrenia according to claim 13, which comprises as an active

ingredient clozapine in a daily dose of 0.7 to 11.5 mg.

16. A therapeutic agent for the memory/learning dysfunctions by

schizophrenia, which comprises as an active ingredient an imide

derivative of the formula [1]:

$$Z-D-N \underset{\diagdown}{\overset{\diagup}{\bigcirc}} G-Ar \qquad [1]$$
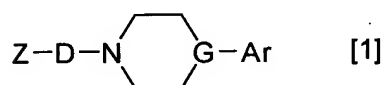
{wherein Z is a group of the formula:
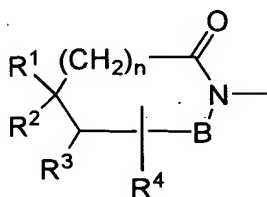
(in which B is a carbonyl or a sulfonyl; R^1 R^2, R^3 and R^4 are

independently a hydrogen atom or a lower alkyl, provided that R^1 and

R^2, or R^1 and R^3 may combine each other to form a hydrocarbon ring, or

R^1 and R^3 may combine each other to form an aromatic hydrocarbon

ring; said hydrocarbon ring may optionally be cross-linked with a lower

alkylene or an oxygen atom; said lower alkylene and hydrocarbon ring

may optionally be substituted by at least one alkyl; and n is 0 or 1),

D is a group of the formula:

$$— (CH_2)_p —A—(CH_2)_q —$$

(in which A is a hydrocarbon ring optionally be cross-linked with a

lower alkylene or an oxygen atom; said lower alkylene and said

hydrocarbon ring may optionally be substituted by at least one alkyl;

and p and q are independently 0, 1 or 2),

G is N, CH or COH, and -Ar is an aromatic heterocyclic group, an

aromatic hydrocarbon group, benzoyl, phenoxy, or phenylthio, or

G is a carbon atom, and -Ar is a biphenylmethylidene,

where said aromatic heterocyclic group, aromatic hydrocarbon group,

benzoyl, phenoxy, phenylthio, and biphenylmethylidene may optionally

5   be substituted by at least one group selected from a lower alkyl, a lower

alkoxy and a halogen atom},

or an acid addition salt thereof.

17.   The therapeutic agent for the memory/learning dysfunctions by

schizophrenia comprising as an active ingredient the imide derivative or

10   an acid addition salt thereof according to claim 16, wherein Ar is an

aromatic heterobicyclic group, naphthyl, benzoyl, phenoxy or

phenylthio, and G is N, CH or COH, or -Ar is a biphenylmethylidene,

and G is a carbon atom (said aromatic heterobicyclic group, naphthyl,

benzoyl, phenoxy, phenylthio and biphenylmethylidene may optionally

15   be substituted by at least one group selected from a lower alkyl, a lower

alkoxy and a halogen atom).

18.   The therapeutic agent for the memory/learning dysfunctions by

schizophrenia comprising as an active ingredient the imide derivative or

an acid addition salt thereof according to claim 16, wherein Ar is an

20   aromatic heterocyclic group condensed with a benzene ring, or naphthyl,

benzoyl, phenoxy or phenylthio (said aromatic heterocyclic group

condensed with a benzene ring, naphthyl, benzoyl, phenoxy, and

phenylthio may optionally be substituted by at least one group selected

from a lower alkyl, a lower alkoxy and a halogen atom), and G is N, CH

25   or COH.

19.   The therapeutic agent for the memory/learning dysfunctions by

schizophrenia comprising as an active ingredient the imide derivative or

an acid addition salt thereof according to claim 16, wherein Z is a group
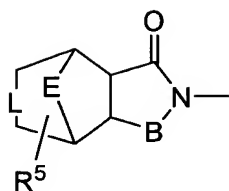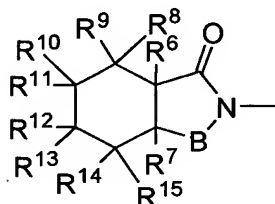
of the formula:

(in which -L- is a single bond or a double bond, E is a lower alkylene optionally substituted by a lower alkyl, or an oxygen atom, R^5 is a hydrogen atom or a lower alkyl, and B is the same as defined in claim 14);
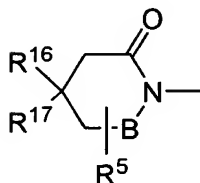
a group of the formula:
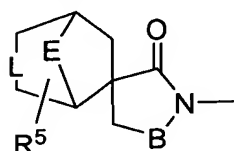
(in which -L-, E, R^5 and B are as defined above);

a group of the formula:

(in which R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} are independently a hydrogen atom or a lower alkyl, or the adjacent two groups of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} may combine each other to form a double bond, and B is as defined above);
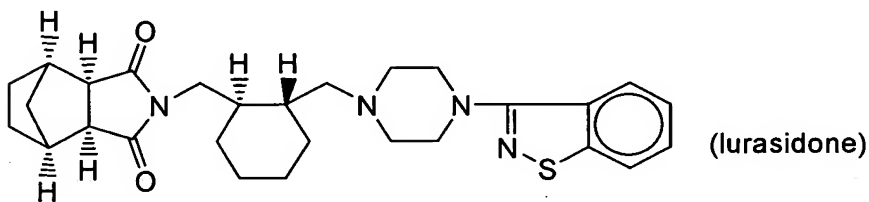
a group of the formula:

(in which R^{16} and R^{17} are independently a hydrogen atom or a lower alkyl, or R^{16} and R^{17} may combine each other to form a saturated

hydrocarbon ring, and R^5 and B are as defined above); or

a group of the formula:
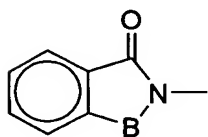
(in which B is as defined above).

5   20.   A therapeutic agent for the memory/learning dysfunctions by

schizophrenia comprising as an active ingredient the imide derivative or

an acid addition salt thereof, wherein the compound of the formula [1]

is lurasidone:

(lurasidone)

10   21.   A therapeutic agent for the memory/learning dysfunctions by

schizophrenia, which comprises as an active ingredient a compound of

the formula (2):

(2)
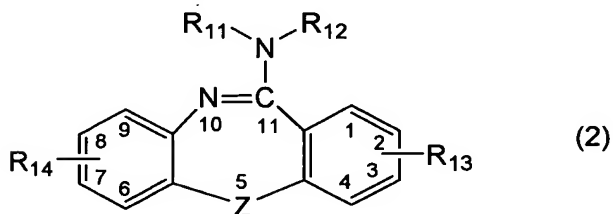
wherein Z is a divalent sulfur, imino, or lower alkylimino;

15   R_{11} is a hydrogen atom or an alkyl having 1 to 5 carbon atoms;

R_{12} is a hydrogen atom, an alkyl having 1 to 5 carbon atoms, a phenyl,

an R_{15}-substituted phenyl, an aminoalkyl having 1 to 5 carbon atoms, a

lower alkylaminoalkyl having 2 to 8 carbon atoms, a lower alkylamino,

an amino, or a lower alkylamino; or

20   R_{11} and R_{12} may combine each other together with N to form a 1-

pyrrolidinyl, piperidino, morpholino, thiomorpholino, 1-piperazinyl, a 4-

lower alkyl-1-piperazinyl, a 4-(hydroxy-lower alkyl)-1-piperazinyl or a 4-(lower alkoxy-lower alkyl)-1-piperazinyl; and

R_{13}, R_{14}, and R_{15} are independently a hydrogen atom, a halogen atom, a hydroxy group, a trifluoromethyl, a lower alkyl, a lower alkoxy, or a

5   lower alkylthio,

or an acid addition salt thereof.